REMARKS

The present paper is presented in response to the Office action mailed December 15, 2003. A response is due March 15, 2003. This paper is filed in accordance with 37 C.F.R. §1.111. Applicants believe that the amendment provided herein above to claim 21 presents the rejected claims in better form for consideration on appeal, and therefore the above-presented amendments may properly be entered in the present application.

I. Status of Claims and Support for Amendments

Claims 1-21, 23 and 25-101 are pending in the instant case. Claims 1-20, and 25-82 were previously withdrawn from consideration as being directed to non-elected subject matter. In the instant application, the Examiner refused to examine claims 96-101 as these claims were allegedly restricted out as groups 28, 30-32, 37 and 50, in the original restriction requirement. Claims 21, 23, 25-27, and 83-95 were examined and variously rejected under 35 U.S.C. §112, first paragraph, for lack of written description, and/or lack of enablement, and under 35 U.S.C. §102(b) or alternatively under 35 U.S.C. §103(a) over Sano et al., (U.S. Patent No. 5,637,490). Applicants respectfully traverse each of the rejections.

Claim 21 has been amended to recite that the peptide being claimed comprises between 6 and 50 amino acid residues and comprises a sequences of at least P_2P_1-$P_1'P_2'$ P_3'. The formula presented in claim 21 is supported in the specification at page 28 and the amino acid residues presented at P3' are supported by the disclosure at page 30 of the specification. Claims 83, 86 and 89 have been similarly amended.

II. Rejection under 35 U.S.C. §112, second paragraph should be withdrawn.

The Patent Office rejected claims 21 and 89 for indefiniteness, alleging that they are virtually identical in scope. Even if true, this allegation merits only an objection, and not a statutory objection. Claims 21 and 89 have each been amended and are now clearly different in scope, rendering the rejection moot.

III. Withdrawal of Claims 96-101 was improper and should be reconsidered

On page 2 of the Office action the Examiner refused to examine claims 96-101, alleging that they were "restricted out as groups 28, 30-32, 37, and 50 in the previous restriction requirement." In response to the original restriction requirement, the Applicants elected Group 56, which included claims 21-27, drawn to a peptide of a generic sequence ***in which P1 is Y***. The Applicants made that election with traverse.

One of the defects of the original restriction requirement -- identified by the applicants in their original traversal -- is that the restriction groups are not mutually exclusive, but rather, are overlapping. (Some peptides fall in six or more different groups!) Each of claims 96-101 recites a specific sequence in which **P1 is Y.** Therefore, the subject matter of claims 96-101 falls within the elected Group 56, and should be examined at this time. The fact that the subject matter of these claims also was designated as corresponding to other restriction groups is correctable by issuing a proper restriction requirement. The Applicants are filing a petition traversing the restriction requirement with this amendment.

IV. The Rejection of the Claims under 35 U.S.C. §112, First Paragraph for Lack of Written Description Should be Withdrawn

The Examiner rejected claims 21, 23, 25-27, 84, and 86-95 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement set forth in that section of the statute. More particularly, the Examiner takes issue with the terms "having 4 to 50 amino acids" or "having 6 to 50 amino acids," and contends that "Applicants do not point out where there is enablement for these limitations in the specification and the examiner has been unable to find these limitations in the specification." (Office action, sentence bridging pages 2 and 3). Applicants respectfully traverse this rejection.

Initially, Applicants point out that notwithstanding the fact that the Examiner has used the term "where there is enablement for these limitations" in articulating the rejection, it is the Applicants' understanding that this rejection is a rejection based on the written description requirement of 35 U.S.C. §112, first paragraph, and not the enablement requirement of 35 U.S.C. §112, first paragraph. These two requirements of the 35 U.S.C.

§112, first paragraph are separate and distinct from one another. *Vas-Cath Inc. v. Mahurkur, 935,* F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991); Revised Interim Written Description Guidelines.

Moving to the guidance in the specification for the terms "having 4 to 50 amino acids" or "having 6 to 50 amino acids," Applicants respectfully refer the Examiner to page 27, lines 27-32 of the specification, where it is stated that:

> "Preferably, the novel peptide substrates for Hu-Asp2, are at least about five amino acids in length, in certain embodiments the novel peptides of the present invention may comprise a contiguous amino acid sequence of about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, or more amino acids."

Applicants further refer to initial claim 1 as originally presented which specifically recited "An isolated peptide comprising a sequence of at least ***four*** amino acids." Given that the initial claims contemplated a peptide of at least four amino acids in length, and that the above-recited paragraph expressly teaches that certain preferred peptides of the invention have a length of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, amino acids, Applicants submit that there is written description for the terms "having 4 to 50 amino acids" or "having 6 to 50 amino acids." Applicants therefore submit that the rejection of the claims for lack of written description should be withdrawn.

V. The Rejection of the Claims under 35 U.S.C. §112, First Paragraph for Lack of Enablement Should be Withdrawn

Claims 21, 23, 25-27 and 83-95 were rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner stated:

> To start with, the majority of the claims are now limited to peptides 4-50 or 6-50 amino acids long. As discussed supra, this embodiment is apparently not disclosed in the instant specification. The embodiments of the claims, even with this limitation, a very broad and have innumerable possibilities. Just because Tyr, Phe and Leu were the

most abundant amino acids at P_1, Asn appeared several times at the P_2 site, Glu, Asp, ala were prominent in the P_1', Val occurred frequently in the P_2' site does not necessarily mean that a rule can be made as in claims 21, 27, 83 and 89 as to the cleavage sites. Just because certain amino acids were 'the most abundant', 'appeared several time', were prominent, and 'occurred frequently' at particular positions does not mean that the applicants can make a general rule using these findings. How residues relate to others around them has to be taken into account. Without an assay for activity one of ordinary skill would not know which were substrates and which were not. None of the claims are limited to the sequences in Table 2, all or even a significant number of embodiments of this formula have not been shown to work as substrates. As to In re Wands, this case involved assaying an antibody against hepatitis B-surface antigen. The case did not involve a general formula comprising numerous possibilities as is the case here.

Applicants respectfully disagree with the Examiner and request reconsideration in light of the following comments and for the reasons already of record.

a. Peptides that are between 4-50 and 6-50 amino acids in length are fully described in the specification as filed.

The Examiner is incorrect in stating the peptides of between 4-50 and 6-50 amino acids are not described in the specification. As discussed is section III above, the peptides that are between 4-50 and 6-50 amino acids in length are specifically contemplated by the specification as filed. Peptides of specific sequences such as SEQ ID NO:144; SEQ ID NO: 141; SEQ ID NO:147, SEQ ID NO:148; SEQ ID NO:145, SEQ ID NO: 143, SEQ ID NO:152, SEQ ID NO:153; SEQ ID NO:190, and SEQ ID NO:191 are presented as particular species of working examples in the specification. Thus, contrary to the Examiner's assertion, the specification **does disclose** "this embodiment," *i.e.*, a genus of peptides that is between 4-50 amino acids or 6-50 amino acids in length.

b. The invention in claims 21, 27, 83 and 89 is enabled because the specification teaches how the residues relate to each other in the context of serving as a substrate for Hu-Asp2, and expressly teaches an assay to identify working embodiments.

The Examiner asserts that "[h]ow residues relate to others around them has to be taken into account." The inventors have done so for this enzyme and described their findings throughout the entire specification, which is directed to teaching how to make better substrates for Hu-Asp2 and these substrates. The specification is directed at changing the residues around a known Asp2 cleavage site to create a new substrate, preferably with a better activity as a Hu-Asp2 substrate as compared to the wild-type substrate for the enzyme, *i.e.*, the wild-type sequence of APP ***which is a known substrate*** for Hu-Asp2 and has a KM-DA sequence at the cleavage site or the Swedish-mutant sequence of APP, ***which is another known substrate*** for the enzyme and has a NLDA sequence at the cleavage site.

Contrary to the Examiner's assertion, knowledge of how frequently a given amino acid appears at a specific position in suitable synthetic substrates provides guidance as to how well-suited the amino acid is for that position in substrate. These assignments of amino acid residues at the specific positions were not made in a vacuum, the Applicants the ***actually tested*** various substrates using a Hu-Asp2 assay. Since the Examiner stated the "without an assay for activity one of ordinary skill could not know which substrates and which are not," Applicants believe that the rejection is based in large part on the misbelief that the application fails to provide a suitable enzymatic assay. However, this assay is described *e.g.*, in the specification at page 41, lines 14-23, where an exemplary experimental assay protocol for determining the cleavage of the peptide substrates by Hu-Asp2 is taught. This **is an exemplary "assay for activity that one of skill in the art would use"** to test whether a given substrate would be a substrate for Hu-Asp2 or not. Because of the activity limitation explicitly set forth in the claims are directed only to functional peptides which are cleaved in a Hu-Asp2 enzyme activity assay; the claims exclude non-functional embodiments.

Using assays known in the art and assays described in the application, one of ordinary skill in the art could readily assess the rate of cleavage of a peptide made from the

Swedish mutant APP, or a wild-type APP, or a substrate of the present invention and compare the rate of cleavage of a peptide substrate of the present invention with either the cleavage rate of the mutant APP or the wild-type APP. This would not involve undue experimentation, but would merely involve routine screening following the teachings of the present invention. Using much of the guidance provided in the instant specification, the authors of Tomasselli et al. (*J. Neurochem.* 84:1006-1017, 2003, attached herewith see especially Table 1 therein), have further corroborated that the substrates of the present invention work as improved substrates for Hu-Asp2, and are cleaved better than either a peptide that contains the Swedish-mutant APP sequence or the wild-type APP sequence. Out of 11 separate peptide sequence tested (peptides 19-29 in Table 1), **all** had rates of cleavage that were better than the rate of cleavage of wild-type APP (KMDA at the cleavage site) and 8 had rates of cleavage that were better than mutant APP (NLDA at the cleavage site).

The Examiner's concern that this case is somehow more difficult than *Wands* because this case involves "a general formula" also is misplaced. The independent claims of the case specify a formula where each position is governed by specific amino acid characteristics, combined with a functional limitation requiring suitability as an enzyme substrate. This claim format is narrower, should be viewed more favorably than, the format in *Wands* that was limited principally by the functional (assay) conditions alone. In fact, as set forth in the next section, the facts of this case (compared to *Wands*) clearly support a conclusion of enablement under the *Wands* factors.

c. The Examiner's focus on Wands' facts is misplaced and Wands should be viewed in light of its holding rather than the underlying subject matter that led to that holding.

While Applicants agree that the ***facts*** of *In re Wands* were that it involved immunoassay methods for the detection of hepatitis B surface antigen by using high-affinity monoclonal antibodies of the IgM isotype, its ***holding*** was not limited in application to those specific facts. Indeed, the United States Patent and Trademark Office training materials with respect to enablement of Chemical/Biotechnological patent applications uses *In re Wands* to set forth "factors to be considered when determining whether there is sufficient evidence to

support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." See http://www1.uspto.gov/web/offices/pac/dapp/oppd/1pecba.htm. The factors that may be considered are:

1. the breadth of the claims,
2. the nature of the invention,
3. the state of the prior art,
4. the level of one of ordinary skill,
5. the level of predictability in the art,
6. the amount of direction provided by the inventor,
7. the existence of working examples, and
8. the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement).

The claims of the present invention are fully enabled as can been seen by an application of each of the factors outlined above. With respect to the scope/breadth of the claims, the training materials advise that "not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. E.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." The claims of the present invention are directed to relatively short peptide sequence (between 6 and 50 amino acids in length.) these sequences have specific defined amino acids at $P_2P_1P_1'P_2'P_3'$ that have been identified by the inventors as producing substrates that are substitutes for (and often are superior to) the natural Hu-Asp2 substrates. Moreover, the claims require that the peptides are cleaved in the Hu-Asp2 assay and as such exclude any peptides that are non-operative, thereby narrowing the breadth of the claims only to functional embodiments. Given the teachings in the specification, the skilled artisan can make other functional substrates and confirm and use them in the assays as described in the specification. Thus, the

first criterion is met in that while there are various permutations of the sequences encompassed by the claims of the invention, such permutations are within the scope of the teaching provided in the specification.

Further, the training materials specifically cite, with emphasis, from the MPEP 2164.08 stating that "[i]f a rejection is made based on the view that the enablement is not commensurate in scope with the claim, **the examiner should identify the subject matter that is considered to be enabled.**" In the instant case, the Examiner has made the blanket statement that the scope of the present claims is "very broad" but, other than indicating that there are "innumerable possibilities," has not provided any definite reasons as to why those possibilities are not enabled by the specification as filed. Applicants assert that the formulae presented in the claims herein define those residues that are important for use of the peptide as a substrate as a Hu-Asp2. The more distal the residue is from the scissile bond, the less important that residue is in affecting the property of the peptide to serve as a substrate for HuAsp2, Furthermore, the peptides being encompassed by the formulae are not as innumerable as the Examiner asserts. The specific residues between *e.g.*, positions P_2 through to P_3 of the peptide do not encompass all possible amino acids at that position but are directed to a much smaller group as defined by the amino acid properties for each position as recited in the claims.

With respect to the second criterion of nature of the invention, the present invention is directed to peptide substrates for use in enzyme reactions. These substrates are made using standard protein chemistry techniques and assayed using an enzyme assay for determining the activity of Hu-Asp. As of the filing date of the specification those of skill in the art could readily make proteins/peptides either through recombinant techniques or through standard solid phase peptide synthesis methods. Indeed, technologies for peptide synthesis are so advanced that there are numerous automated peptide synthesizers that are commercially available. As for the assay for Hu-Asp2 activity, it is expressly taught at page 41, lines 14-23, and is based on assays that are already known to those of skill in the art. Thus, much like the level of skill of the artisan in *In re Wands*, the level of skill in the art (criterion 4) in protein synthesis and running enzyme assays is very high.

With respect to the state of the art (criterion 3), it is noted that prior to the present invention, in order to determine the activity of a preparation of Hu-Asp2, the skilled artisan employed the wild-type (KMDA-containing), or Swedish mutant (NLDA-containing), APP as substrates. In comparison to the preferred substrates of the present invention the prior art substrates are cleaved by the enzyme at a ***much slower*** rate. Indeed, as can be seen in Tomasselli *et al.* (2003) each of peptides 19-29 was a better substrate for the enzyme than the wild-type APP sequence. Most of the peptides in Tomasselli *et al.* are expressly recited in the present application and thus are working examples (satisfying criterion 7 of *Wands*) of the invention, and the remainder of the peptides may be derived from the disclosure of the invention which teaches the preferred amino acid residues that should be provided around the β-secretase cleavage site.

There is substantial guidance in the specification (criterion 6) as to how to proceed with producing substrates for Hu-Asp2. More particularly, the specification has taught that the presence of certain residues around the scissile bond of the substrate produces substrates that are better than the wild-type APP sequence, thereby providing significant guidance as which peptides should be produced for use in the present invention (criterion.

As for providing working examples (criterion 7), the specification provides a teaching that at least each of sequences SEQ ID NO:144; SEQ ID NO: 141; SEQ ID NO:147, SEQ ID NO:148; SEQ ID NO:145, SEQ ID NO: 143, SEQ ID NO:152, SEQ ID NO:153; SEQ ID NO:190, and SEQ ID NO:191 serves as a better substrate for Hu-Asp2 than peptides that have the wild-type APP sequence (KMDA) or even Swedish mutation sequence (NL-DA). For example, the specification teaches that a sequence SEVSYEVEFR has a relative cleavage rate of 141% of the rate of SEVNLDAEFR (see Table 4). This teaches that making the P_1 residue of the substrate a tyrosine residue and for example ensuring that the P_2 residue is a serine residue and the $P_{1'}$ residue is glutamic acid residue and $P_{2'}$ is a valine, one produces a more useful substrate for Hu-Asp2 than a peptide containing the Swedish-mutation, which in the art is recognized as a better substrate than a peptide containing the wild-type APP sequence. Moreover, in Table 5 is it demonstrated that N-terminally extending the SEVSYEVEFR produces an even better substrate than the SEVSYEVEFR

alone. There are numerous other peptides of the invention that are specifically exemplified in the sequence listing and the specification that fall within the scope of the peptide claims.

A detailed review of the disclosure shows that the inventors have provided copious guidance as to exactly which residues to select at the positions around the scissile bond to produce substrates that are more effective than the wild-type and have presented specific working examples of how to make and test such substrates. The quantity of experimentation needed (criterion 8) to make or use the substrate invention based on the content of the disclosure is thus much less than even that which was considered enabled in *In re Wands*. To make further embodiments in the present case, one synthesizes peptides using automated synthesizers and according to the guidance in the specification, and test them in an activity assay such as the one exemplified in the specification. This is even simpler than the situation found in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), where the court found that identifying antibodies that are specific for HBsAg antigen requires nothing more than routine screening and reversed the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement. Peptide synthesis used in the present invention is an automated, routine and fast procedure, and the protease assays can be run rapidly, in small scale high throughput format. The present specification provides guidance as to the sequences and teaches the *in vitro* screens that can be used to test those sequences. In contrast, the technology of *In re Wands* involves a much slower technique that relies on immunization of animal, laborious isolation and screening of hybridomas and ultimate isolation and testing of operative and inoperative antibodies. Applicants fail to see how it would require undue to make and use substrates of a specified sequence as taught and claimed in the present application, when the courts have expressly recognized that screening for antibodies (which are proteins) against a given antigen does not require undue experimentation, even when the hybridomas are not identified.

Applicants believe that the claims of the present invention are fully enabled and Applicants therefore request that the rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

VI. The Rejection based on Sano *et al.* should be withdrawn

The Examiner rejected claims 21, 23, 25-27, 83-85 and 89 under 35 U.S.C. §102(b) as allegedly anticipated by or in the alternative, under 35 U.S.C. §103(a) as being obvious over Sano et al., U.S. Patent No.5,637,490. Applicants respectfully traverse.

a. The claims are novel over the Sano et al. disclosure

Claims 21, 83, 86, and 89 are the only independent claims presently under consideration. The remaining claims under consideration depend from each of these claims. Therefore, Applicants address the patentability of the independent claims because the dependent claims, which incorporate all of the features of the independent claims, are patentable for at least the same reasons as the independent claims.

It is axiomatic that in order to anticipate a claim, the single prior art reference must teach every element of the claim. M.P.E.P. §2131. Thus, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Using this well-established legal premise as a guide, it is clear that none of the independent claims under consideration in the instant application are anticipated by the Sano *et al.*

Claim 21 has been amended to specifically define a fifth amino acid (P_3' comprises an amino acid selected from the group consisting of E, G, F, H, cysteic acid and S) that is not present in the SEQ ID NO: 4 peptide of Sano relied upon for the rejection. (In Sano, the amino acid in position P_3' is tyrosine.) Thus, the rejection of claim 21 and every claim dependent therefrom (e.g., claims 23, 25, 26) should be withdrawn.

Claim 27 recites a polypeptide that includes a cleavage site (a) and a transmembrane domain (b). The peptide disclosed in Sano and cited by the examiner does not have a transmembrane domain (b), so the rejection should be withdrawn. The Patent Office says that it cannot determine whether Sano's peptide has a transmembrane domain, but this is incorrect. The Sano reference describes the fucosidase enzyme as soluble in an

aqueous buffer, rather than as a transmembrane protein. Moreover, the Sano peptide is only 14 amino acids long and the P_2P_1--$P_1'P_2'$ sequence falls in the middle of the peptide. It is well known that transmembrane domains are about 20 amino acids in length -- a condition that cannot be met by SEQ ID NO:4 of Sano.

Claim 83 recites a peptide of a specified formula that comprises a detectable label and a quenching moiety, wherein cleavage of the peptide between P1 and P1' separate the quenching moiety from the label to permit detection of the label. The Sano reference fails to disclose or suggest a label, let alone a label with a quenching moiety. The peptide cited in Sano was nothing more than a lysyl endopeptidase reaction product, and Sano fails to disclose or suggest any use for the peptide. Notably, there is no disclosure or suggestion to use the peptide as a peptidase substrate and no motivation whatsoever to attach any label to it, let alone a label and quenching moiety as recited in claim 83. For all of these reasons, the rejection should be withdrawn. Claims 84-85 depends from claim 83 and is patentable over Sano for reasons set forth in the preceding paragraph.

Claim 89 has been amended to require that the peptide of the claim include a label. As explained in the preceding paragraph, Sano fails to disclose or suggest or provide any motivation for including a label on its SEQ ID NO: 4 peptide. The Patent Office's position is that "the addition of a label to aid in the assay would have been obvious." However, there is no statement in Sano about a label and no statement in Sano to use the peptide in the Applicant's HuAsp2 protease assay or any other assay. The Patent Office's reviewing court has stated in no uncertain terms that it is reversible error to make obvious rejections with unsupported assertions about what would have been obvious, without pointing to disclosures in the prior art and/or motivations for combining or modifying references. See *In re Sang Su Lee*, 277 F.3d 1338; 61 U.S.P.Q.2D, 1430 (Fed. Cir. 2002).

b. The claims are non-obvious over the Sano et al. disclosure

As discussed above, Sano *et al.* fails to anticipate any of the claims of the present application. Moreover, the Sano *et al.* patent also does not render obvious the claims

of the instant application. As Applicants have pointed out in the previous response, in order to render a claimed invention obvious, the cited art not only has to (1) teach or suggest every element of the claimed invention, the cited reference, or combination of references, (2) must also provide some suggestion or motivation to modify the reference(s) to arrive at the claimed invention and (3) there must be some reasonable expectation of the success of such modification of the reference(s). *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). The motivation and the reasonable expectation of success must come from the art and not from the Applicants' own disclosure. As stated in MPEP 2143, all three of the above criteria ***must*** be met in order to properly establish *prima facie* obviousness. Even a cursory review of the Sano reference reveals that it fails to meet the criteria for establishing *prima facie* obviousness.

In analyzing the claims of the instant application, it should be noted that the claims are directed to isolated peptide substrates that comprise specific formulae of specific amino acid lengths. Other claims are directed to peptides that have been modified to permit the detection of cleavage of the peptide by Hu-Asp2. The Examiner asserted that the disclosure of SEQ ID NO:4 of Sano may render obvious these claims of the present invention. Applicants respectfully disagree.

The entire disclosure of Sano *et al.* is directed to a fucosidase protein, and SEQ ID NO:4 is a 20 amino acid fragment of that protein (See column 8 lines 5-7). There is no indication in the Sano document that this protein may act as a substrate for Hu-Asp2. As discussed above, the peptide sequences of the present invention are not anticipated by SEQ ID NO:4. There is no suggestion in the reference that one of skill in the art could or should produce a peptide of SEQ ID NO:4 for the purpose of using it in an assay for Hu-Asp2 activity, let alone any suggestion that one skilled in the art should take the peptide of SEQ ID NO:4 of Sano et al ***and modify it*** to produce the peptides having a sequence recited in any one of the claims of the present invention and use those modified sequences in assays for Hu-Asp2 activity. Hence, the Examiner has not established that the sequences themselves are taught by the prior art. Absent these teachings in the cited art, any general disclosure of labeling peptides is immaterial and the peptide substrates of the present invention cannot be

rendered obvious by the sequence of SEQ ID NO:4 of Sano *et al.* Thus, because there is no suggestion to produce the novel substrates of the present invention, there is no motivation to modify the peptides in the manner suggested by the Examiner.

Moreover, given that there is a complete lack of suggestion to produce peptide substrates of the present invention, there would be no expectation of success of producing a peptide substrate of the claimed invention. Again, there is no teaching in the cited art that it would be desirable to produce the claimed peptides as substrates for Hu-Asp2. Thus, the cited prior art failed to appreciate that there was any need for such peptides. In the absence of such a teaching, there would be no reason for one of skill in the art to produce such substrates or for that individual to expect such compounds to be useful in any Hu-Asp2 related assay. The only motivation to produce the substrates, and the only expectation of success of producing the same, is derived from the instant specification and not from the prior art. The Examiner's approach to alleging the obviousness of the instant claims is based on an improper premise of hindsight reconstruction from the Applicants' own disclosure. The Courts have clearly stated that this is improper. ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W. L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220USPQ 303 (Fed. Cir. 1983)).

VII. The Rejection based of claims 83 and 85 under 35 U.S.C. §103(a) should be withdrawn

The Examiner rejected claims 83 and 85 under 35 U.S.C. §103(a) as obvious over any one of Sermjian *et al.* (*J. Mol. Biol.* 207:1-13, 1989), Van Camp *et al.*, (*Proc. Nat'l. Acad. Sci.*, 87:9903-9907, 1990), Lowell et al., (*J. Biol. Chem.*, 261(18):8442-8452, 1986) or Sellar *et al.*, (*J. Biol. Chem.*, 266(6):3505-3510, 1991).

The Examiner indicated that "it would have been obvious to use a detectable label on the substrate in view of the general knowledge of one of ordinary skill in the art. The motivation would have been to readily measure the cleavage of the substrate. The

cleavage rate of Hu-Asp2 on the instant substrates is not known but since the reference meets the requirement of claim 83, it is presumed that this rate is as in claim 85, absent convincing proof to the contrary." (Office action, page 6). Applicants respectfully traverse.

None of the references that are relied upon by the Examiner either teach or suggest that any of the peptides described therein could or should be used as substrates for any protease assay, let alone a Hu-Asp2 enzyme activity assay. Accordingly, there is no motivation to modify the prior art peptides or polypeptides to improve their utility as substrates. Nevertheless, the Examiner stated that "motivation would have been to readily measure the cleavage of the substrate" for the skilled artisan to make the peptides of the invention. Applicants respectfully submit that this falls into the very same trap of the "insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" that the Court in *W.L. Gore & Assoc.* warned against.

Furthermore, as explained above, and in the previous response, the first requirement for establishing *prima facie* obviousness is to point to a teaching in the art that teaches each element of the claimed invention. The substrates of claim 83 expressly require that the peptides comprise a detectable label and a quenching moiety. Applicants have not found these requisite features in any of the teachings of Sermjian *et al.*, Van Camp *et al.*, Lowell et al., (*J. Biol. Chem.*, 261(18):8442-8452, 1986) or Sellar *et al.*, (*J. Biol. Chem.*, 266(6):3505-3510, 1991. As indicated above, the motivation cited by the Examiner to modify the teachings of these references to add a detectable label to any peptide that one of skill in the art might make is based on improper hindsight reconstruction and no prior art teaching whatsoever. Thus, it is an ineffective reason for establishing *prima facie* obviousness. The Federal Circuit has advised that the "PTO must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious. The Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor ***and no knowledge*** of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. While skill level is a component of the inquiry for the suggestion to combine, a lofty level of skill alone does not suffice to supply a motivation to

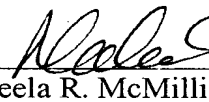
combine. Otherwise a high level of ordinary skill in the art field would almost always preclude patentable inventions." *In re Roufett*, 149 F.3d 1350, 47 USPQ2d 1453, 1458, 1459 (Fed. Cir. 1998). The law requires that the Examiner either identify these required features in the cited art, and show reasons that the skilled artisan would make the peptides of the present invention ***in the absence of the knowledge afforded by the present specification***, or withdraw the rejection.

VIII. Conclusions

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

Dated: March 15, 2004

Respectfully submitted,

By 

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